Mantle cell lymphoma of the gastrointestinal tract 
(lymphomatous polyposis)

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Virtually all primary gastrointestinal lymphomas are non-Hodgkin’s in type, while primary gastrointestinal Hodgkin’s disease is very rare. A number of classification systems for lymphoma have been compared, continue to evolve and have been summarized elsewhere, especially from a pathological perspective (1,2). Isaacson (2) provided a very valuable operational definition for primary gastrointestinal lymphoma: that form of lymphoma with the main bulk of disease in the gastrointestinal tract, necessitating direction of treatment to that site. In Canada, as in other western countries, the most common sites of primary lymphoma in the gastrointestinal tract are the stomach and small intestine; only rarely are the esophagus or colon involved.

The types of non-Hodgkin’s gastrointestinal lymphoma include T cell-derived lymphomas usually associated with celiac disease (1-5) and termed ‘enteropathy-associated T cell lymphomas’, as well as various B cell types. The main B cell types of primary gastrointestinal lymphoma include low grade...
and high grade mucosa-associated lymphoid tissue (MALT) B cell lymphomas, mainly arising in the stomach or small intestine (6,7); immunoproliferative small intestinal disease, reported almost always, but not exclusively, from Middle Eastern countries and usually associated with the synthesis of abnormal alpha heavy chains (8); Burkitt’s lymphoma or Burkitt’s-like lymphoma, often associated with Epstein-Barr virus genomes, and usually presenting in an endemic or sporadic fashion with ileocecal involvement (9); and lymphomatous polyposis or mantle cell lymphoma, a rare type of B cell lymphoma of the gastrointestinal tract that may arise initially in peripheral lymph nodes (10).

The patient described in this report initially presented with clinical features of a lymphocytic lymphoma in a tonsillar node. Later, extensive involvement with lymphomatous polyposis was observed through his entire gastrointestinal tract following his presentation with diarrhea. In addition to the documentation of lymphomatous polyposis in the present report, recent molecular genetic data suggest that distinction

Figure 1) Moderately well differentiated lymphocytic lymphoma in a tonsillar node (hematoxylin and eosin, x140)

Figure 2a) Rectal biopsy showing melanosis coli with pigmented macrophages in the lamina propria. Lymphoid cells are morphologically monotonous and diffusely increased in the lamina propria and submucosa (hematoxylin and eosin, x131)

Figure 2b) Rectal biopsy showing melanosis coli with pigmented macrophages in the lamina propria. Lymphoid cells are morphologically monotonous and diffusely increased in the lamina propria and submucosa (hematoxylin and eosin, x133)

Figure 2c) Lymphoid cells in the rectal mucosa are monomorphic with atypical, and small- and medium-sized lymphocytoid cells, some with crinkled or slightly clefted nuclear membranes. Other lymphoid cells have scant cytoplasm and angulated nuclei. Occasional larger, irregular cells are seen with more prominent nuclei (hematoxylin and eosin, x546)
from other forms of primary B cell gastrointestinal lymphomas may be critical, particularly from the MALT-type lymphomas because these are reported to be susceptible to Helicobacter pylori eradication therapy (7).

**CASE PRESENTATION**

A 74-year-old male was investigated for hoarse voice, Horner’s syndrome and enlarged tonsils. Cervical adenopathy was also present. Laboratory studies demonstrated the following: hemoglobin, 117 g/L (normal 140 to 160); white blood cell count, 13.7 x 10^9/L with 66% lymphocytes; and normal carotene, iron and iron binding capacity, folic acid and vitamin B12. Fecal bacterial cultures, Clostridium difficile toxin assays and studies for parasites were negative. Sigmoidoscopy showed minimally friable mucosa with melanosis coli; in addition, mucosal nodularity was present. Biopsies revealed melanosis coli with pigmented macrophages and focal mild inflammatory change. In some areas, monotonous collections of lymphoid cells typical of malignant lymphoma were seen extending through the surface epithelium and associated with focal micro-ulceration; in other areas, similar lymphomatous infiltrates were present extending through the mucosa and submucosa (Figure 2).

Barium enema revealed abnormal-appearing haustral folds through the entire colon. In the cecum, a lobulated filling defect was present in the base of the appendix. A small intestinal biopsy demonstrated a focal lymphomatous infiltrate extending from the lamina propria into the submucosa. Villi were present without changes of celiac disease. Despite treatment with total body irradiation, the patient’s clinical course became complicated by pneumonia and he died less than three months after the initial detection of lymphoma in his gastrointestinal tract.

Postmortem examination revealed diffuse lymphomatous polypoid involvement through the entire gastrointestinal tract along with enlarged cervical, mediastinal and mesenteric lymph nodes. In the esophagus, the mucosa was studded with tiny white nodules containing lymphoma (Figure 3). The gastric rugae were thickened and coarse (Figure 4a), and, despite postmortem autolytic changes, diffuse lymphomatous infiltrate involving the mucosa and submucosa was evident (Figure 4b). Some focal ulcerations were evident in the distal antrum; *H pylori* were not seen. Multiple lymphomatous polypoid lesions were present in the small intestine (Figure 5). The cecum and remainder of the distal large intestine were studded with white nodular lesions on a background of melanosis coli (Figure 6); these nodules contained lymphoma. The base of the appendix was also thickened and polypoid with lymphomatous infiltration. All lymph nodes were largely replaced with neoplastic lymphoid cells. In addition, microscopic lymphomatous infiltrates were detected in the spleen, liver and kidney.

Microscopic examination revealed similar features in all gastrointestinal tract sites: a lymphocytoid neoplastic infiltrate consisting of a monomorphic population of small lymphocytes, some with a crinkled or slightly clefted nuclear membrane. Sheets of atypical small- to medium-sized lymphoid cells were also present with scant cytoplasm and angulated nuclei. Within these cells were larger, irregular cells with more prominent nucleoli. Immunophenotypic studies showed CD5+, but also CD10- and CD23-, which are characteristic of mantle cell lymphoma (1,10,11).

One month later the patient was referred because of watery diarrhea (up to eight episodes/day) and urgency. There was no abdominal pain or rectal bleeding. Laboratory studies included hemoglobin, 118 g/L; white blood cell count, 21.0x 10^9/L with 66% lymphocytes; and normal carotene, iron and iron binding capacity, folic acid and vitamin B12. Fecal bacterial cultures, Clostridium difficile toxin assays and studies for parasites were negative. Sigmoidoscopy showed minimally friable mucosa with melanosis coli; in addition, mucosal nodularity was present. Biopsies revealed melanosis coli with pigmented macrophages and focal mild inflammatory change. In some areas, monotonous collections of lymphoid cells typical of malignant lymphoma were seen extending through the surface epithelium and associated with focal micro-ulceration; in other areas, similar lymphomatous infiltrates were present extending through the mucosa and submucosa (Figure 2).
DISCUSSION

The patient presented with a very extensive lymphoproliferative disorder first observed in tonsillar nodes, and later found in the colon and then found widely disseminated throughout the entire gastrointestinal tract. Clinical and pathological features described elsewhere (1,2) that were seen in this patient were typical of lymphomatous polyposis or mantle cell lymphoma. The patient was an elderly male with a nodular pangastrointestinal neoplastic process that proved to be lymphoma; lymphomatous polyposis or mantle cell lymphoma is usually found in males over age 55 years, and any part of the gastrointestinal tract may be involved, usually in the ileocecal region. The cells in lymphomatous polyposis may appear as small cleaved cells, resemble centrocytes and have the CD5-positive immunophenotype, derived from mantle zone B cells (1,10,11). Often, as in the patient here, presentation occurs at an advanced stage of the lymphoma, frequently with generalized adenopathy and involvement of spleen, liver and Waldeyer’s ring (12,13). In addition, the peripheral blood may be involved in up to 40% (12,13), and the gastrointestinal mucosa and/or submucosa in up to 20%, of all diagnosed patients (14). Mantle cell lymphoma is apparently a moderately aggressive form of lymphomatous disease, with median survival ranging from about 30 to 60 months; however, occasional patients have a more fulminant course (15). This contrasts with the typical clinical and pathological features of other B cell extranodal lymphomas, especially MALT-type lymphomas. These usually occur in younger patients, extensively involve the stomach, often with lymphomatous or recurrent ulceration, and are typically associated with detection of H pylori (1,2,6,7). Less frequently, the small intestine is involved. In very rare patients, esophageal or colonic involvement may be seen. With colorectal involvement from a B cell lymphoma, a history of inflammatory bowel disease may also be present, as recently reviewed (16). Although MALT-lymphoma cells bear a close resemblance to small cleaved cells and are ‘centrocyte-like’, localized epithelial invasion by lymphoid cell aggregates, often with epithelial destruction, occurs. These ‘lymphoepithelial lesions’ (2) are observed in MALT-type lymphomas and characteristically are negative for the CD5 immunophenotype (1,2, 10,11). Precise distinction of MALT lymphomas from other B cell lymphomas, such as mantle cell lymphomas, may be important since recent studies have implicated H pylori in the pathogenesis of MALT-type lymphomas and provide evidence that antibiotic eradication of the organism may result in regression of gastric MALT lymphomas (7).
Earlier classifications of lymphoma used different terms to describe mantle cell lymphoma. The term ‘centrocytic lymphoma’ was originally used because the centrocyte (ie, small, cleaved cell of the germinal centre) was believed to be the cell of origin of the lymphoma (17). Others classified this lymphoma as an ‘intermediate lymphocytic lymphoma’ (18,19). The term ‘mantle cell lymphoma’ was introduced in 1982 (20) because the tumour was believed to begin in normal primary lymphoid follicles and the mantles of secondary follicles (10). The term was formally adopted in 1992 (10). Later, immunohistochemical studies described the profile of mantle cell lymphoma with surface immunoglobulin (Ig) M and sometimes IgD, as well as either kappa or lambda light-chain restriction. Other pan-B cell antigens may be present, as well as other antigens, including CD5. These immunophenotypic features have aided the differentiation of mantle cell lymphoma from other low grade B cell lymphomas, including MALT and follicular centre cell lymphomas, as well as chronic lymphocytic leukemia (10,11).

REFERENCES
24. Rimokh R, Berger F, Cormillet P, et al. Break in the BCL-1 locus on the long arm of chromosome 11, has been detected in most patients with mantle cell lymphoma, but not in other lymphoma subtypes (21-24). Recent molecular genetic studies have also indicated that this translocation results in overexpression of a gene known as PRAD1, which encodes for cyclin D-1, a cell-cycle protein not normally expressed in lymphoid cells (25,26). Recently, testing using polyclonal antibodies on paraffin-embedded sections has shown nuclear cyclin-D1 protein in virtually all cases of mantle cell lymphoma (27); this protein is apparently not detectable in normal lymphoid tissue or in the tissue from patients with other forms of non-Hodgkin’s lymphoma (27).